The influence of physical activity on the incidence of breast cancer

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Abstract

INTRODUCTION: Breast cancer is a complex entity, as it is not only influenced by genetics, but also by, inter alia, environmental factors and lifestyle choices. Physical activity has been known to have a positive influence on health in general, not only on e.g. cardiovascular or orthopedic diseases, but on malignancies as well. In this paper, we will assess the influence of physical activity on the incidence of breast cancer.

METHODS: We searched Pubmed, Embase and Cochrane Library up to 12/10/2021. We identified 1384 records and included 8. For our search we used the Problem (general populace), Intervention (physical activity), Comparison (no physical activity), Outcome (incidence of malignancies) process (PICO). Our inclusion criteria were: articles discussing the incidence of malignancies in relation to physical activity, systematic reviews or meta-analyses, articles written in the English or Dutch language and articles studying adults starting from the age of 18. Exclusion criteria were: studies that were not a systematic review or meta-analysis, articles studying diseases other than malignancies, articles studying patients with malignancies in their medical history and articles discussing minors or animals. After additional quality appraisal of the 8 selected articles, 4 were excluded due to being lower in quality.

RESULTS: Analysis in both pre-and postmenopausal women show a significant effect of physical activity on the reduction of breast cancer incidence (incidence reduction of about 20% in both groups). BMI is a great confounder and has a great influence on these results. The effect in women with a BMI higher than 25 kg/m^2 is smaller to insignificant, and the effect in women with a BMI higher than 30 kg/m^2 is even negligible. Women with pathogenetic BRCA1/2 mutations experience a similar risk reduction as women without these mutations. The protective effect of physical activity is relative to the amount of physical activity, with a dose-response relationship diminishing at 30 MET-h/week. The timing of physical activity is of lesser importance.

CONCLUSION: Physical activity has a positive effect on the reduction of the incidence of breast cancer in women. However, more studies of higher quality and with a higher-quality evidence load are needed to confirm this conclusion.

Abstract (Nederlandse versie)

INTRODUCTIE: Borstkanker is een complexe aandoening dewelke door verschillende factoren wordt beïnvloed, waaronder genetica, omgevingsfactoren en levensstijl. Lichaamsbeweging heeft een gekende positieve invloed op de algemene gezondheid, niet alleen op bijvoorbeeld cardiovasculair en orthopedisch vlak, maar ook op verschillende maligniteiten. In deze paper onderzoeken we de invloed van lichaamsbeweging op de incidentie van borstkanker.

METHODEN: We doorzochten Pubmed, Embase en Cochrane Library op 12/10/2021. Uit de 1384 artikels die we vonden, includeerden we 8 artikels. Voor onze zoektocht gebruikten we als PICO: Problem (general populace), Intervention (physical activity), Comparison (no physical activity), Outcome (incidence of malignancies). Onze inclusiecriteria waren: artikels die het verband tussen de incidentie van maligniteiten en lichaamsbeweging beschreven, systematische reviews of meta-analyses en artikels geschreven in het Engels of het Nederlands. Exclusiecriteria waren: studies die geen systematische reviews of meta-analyses uitmaakten, studies die andere ziektes dan maligniteiten beschreven, studies die patiënten met maligniteiten in hun medische voorgeschiedenis onderzochten en artikels die minderjarigen of dieren

beschreven. Na kwaliteitscontrole van 8 geselecteerde artikels, werden nog eens 4 artikels geëxcludeerd vanwege een te lage kwaliteit.

RESULTATEN: Analyse in zowel premenopauzale als postmenopauzale vrouwen toont een significant effect van lichaamsbeweging op de vermindering van borstkankerincidentie (met name een incidentievermindering van ongeveer 20% in beide groepen). BMI is een grote confounder en beïnvloedende factor bij deze resultaten. Zo is het effect bij vrouwen met een BMI hoger dan 25 kg/m² kleiner tot insignificant, en het effect bij vrouwen met een BMI hoger dan 30 kg/m² zelfs verwaarloosbaar. Vrouwen met pathogene BRCA1/2 mutaties ervaren een gelijkaardige reductie van borstkankerincidentie als vrouwen zonder deze mutaties. Het beschermende effect van lichaamsbeweging is afhankelijk van de hoeveelheid van de lichaamsbeweging, met een dosis-responsrelatie die vermindert bij meer dan 30 MET-h/week. De timing van de lichaamsbeweging is van minder belang.

CONCLUSIE: Lichaamsbeweging heeft een positieve invloed op de vermindering van de incidentie van borstkanker bij vrouwen. Echter zijn er meer studies van hogere kwaliteit en met een hogere bewijskracht nodig om deze conclusie te bevestigen.

Introduction

Breast cancer is a complex entity. Not only is it influenced by genetics, but also by, inter alia, environmental factors and lifestyle choices. Physical activity has been known to have a positive influence on health in general, not only on e.g. cardiovascular or orthopedic diseases, but on malignancies as well.(1) In this paper, we will assess the influence of physical activity on the incidence of breast cancer.

Several articles, reviews and meta-analyses have been published on the topic of physical activity and its influence on specific malignancies. The effect of physical activity on malignancies is not easily evaluated, in part because there are different ways of describing the amount of the physical activity.(2) In some studies, a distinction is made between occupational and non-occupational exercise.(3)

The initial setup of this paper was to provide an update on the effect of physical activity on the incidence of malignancies. Due to the large number of studies we found after our initial search, we decided to narrow our focus to one specific form of cancer. We chose breast cancer because of its high prevalence in the female population and its high impact on women of a relatively young age. The effect of physical activity on other types of malignancies are to be discussed in separate studies.

Methods

Search Strategy

To formulate our clinical question, we used the Population, Intervention, Comparison, Outcome (PICO) process. Our population included the general populace, our intervention was defined as “physical activity”, our comparison can be described as “no physical activity” and our outcome was the “incidence of malignancies”.

P: General Populace
I: Physical activity
C: No physical activity
O: Incidence of malignancies

The search was conducted using three databases: Pubmed, Embase and Cochrane Library Search Manager. The last search of articles was conducted on the 12th of October 2021. The full search queries are provided in table 1. Keywords included in the search were: physical activity, exercise, cancer, malignancies, meta-analysis, systematic review. We searched specifically for reviews, systematic reviews and meta-analyses using the search term strategy developed by Avau et al.(4)

The search strategy was designed to find articles concerning all kinds of malignancies. Due to the large amount of studies and the wide variety of topics, we decided to focus on breast cancer alone. This decision was made after filtering the articles found with the described search strategy and therefore our search strategy is not specifically focused on breast cancer.

After filtering for duplicates, titles, and abstracts, respectively 882, 239 and 111 articles were identified. After filtering for text, 8 articles were included.

Database	Search query	Date	Articles found
Pubmed	("Exercise"[Mesh] OR exercis*[TIAB] OR "physical activity"[TIAB]) AND ("Primary Prevention"[Mesh] OR prevention[TIAB]) AND ("Neoplasms"[Mesh] OR neoplasm*[TIAB] OR cancer*[TIAB] OR malignanc*[TIAB]) AND (("Meta-Analysis as Topic"[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR "Meta-Analysis"[PT] OR "Systematic Review"[PT] OR "Systematic Reviews as Topic"[Mesh] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR "Review Literature as Topic"[Mesh]) OR (cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR "science citation index"[TIAB] OR bids[TIAB] OR cancerlit[TIAB]) OR (reference list*[TIAB] OR bibliograph*[TIAB] OR handsearch*[TIAB] OR "relevant journals"[TIAB] OR manual search*[TIAB]) OR (("selection criteria"[TIAB] OR "data extraction"[TIAB]) AND "Review"[PT])) NOT ("Comment"[PT] OR "Letter"[PT] OR "Editorial"[PT] OR ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))))	12-10-2021	217
Embase	('exercise'/exp OR exercis* OR workout:ab,ti OR physical activity) AND ('primary prevention'/exp OR prevention) AND ('neoplasms'/exp OR cancer* OR malignanc*) AND (('meta analysis (topic)'/exp OR 'meta analysis'/exp OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR (systematic NEXT/1 review*):ab,ti OR (systematic NEXT/1 overview*):ab,ti) OR (cancerlit:ab,ti OR cochrane:ab,ti OR embase:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR cinahl:ab,ti OR cinhal:ab,ti OR 'science citation index':ab,ti OR bids:ab,ti) OR ((reference NEXT/1 list*):ab,ti OR bibliograph*:ab,ti OR handsearch*:ab,ti OR (manual NEXT/1 search*):ab,ti OR 'relevant journals':ab,ti) OR (('data extraction':ab,ti OR 'selection criteria':ab,ti) AND review/it)) NOT (letter/it OR editorial/it OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))	12-10-2021	796
Cochrane	ID Search Hits #1 MeSH descriptor: [Exercise] explode all trees 26197 #2 MeSH descriptor: [Primary Prevention] explode all trees 4354 #3 MeSH descriptor: [Neoplasms] explode all trees 83140 #4 MeSH descriptor: [Prevalence] explode all trees 4714 #5 exercis*:ti,ab,kw 115900 #6 MeSH descriptor: [Incidence] explode all trees 10313 #7 cancer*:ti,ab,kw 1056 #8 neoplasm*:ti,ab,kw 716 #9 incidence*:ti,ab,kw 126805 #10 (#1 OR #5) AND (#2 OR #4 OR #6 OR #9) AND (#3 OR #7 OR #8)	12-10-2021	371

Table 1: search queries

Eligibility criteria

Two reviewers (HM and GM) selected articles independently. A comparison was made between selected studies, and the final articles were chosen in mutual agreement. Only articles reporting on the association between breast cancer incidence and physical activity were included. Other inclusion criteria were articles written in the English or Dutch language and articles pertaining to adults from the age of 18. The study designs included were systematic reviews and meta-analyses. A few reviews were included as well, as the quality and applicability were deemed adequate by both reviewers.

Inclusion criteria:

- Articles discussing the incidence of malignancies in relation to physical activity.
- Systematic reviews or meta-analyses.
- Articles written in the English or Dutch language.
- Articles studying adults starting from the age of 18.

Exclusion criteria:

- Studies that were not a systematic review or meta-analysis.
- Articles discussing diseases other than malignancies.
- Studies including patients with malignancies in their medical history.
- Studies including minors.
- Studies including animals.

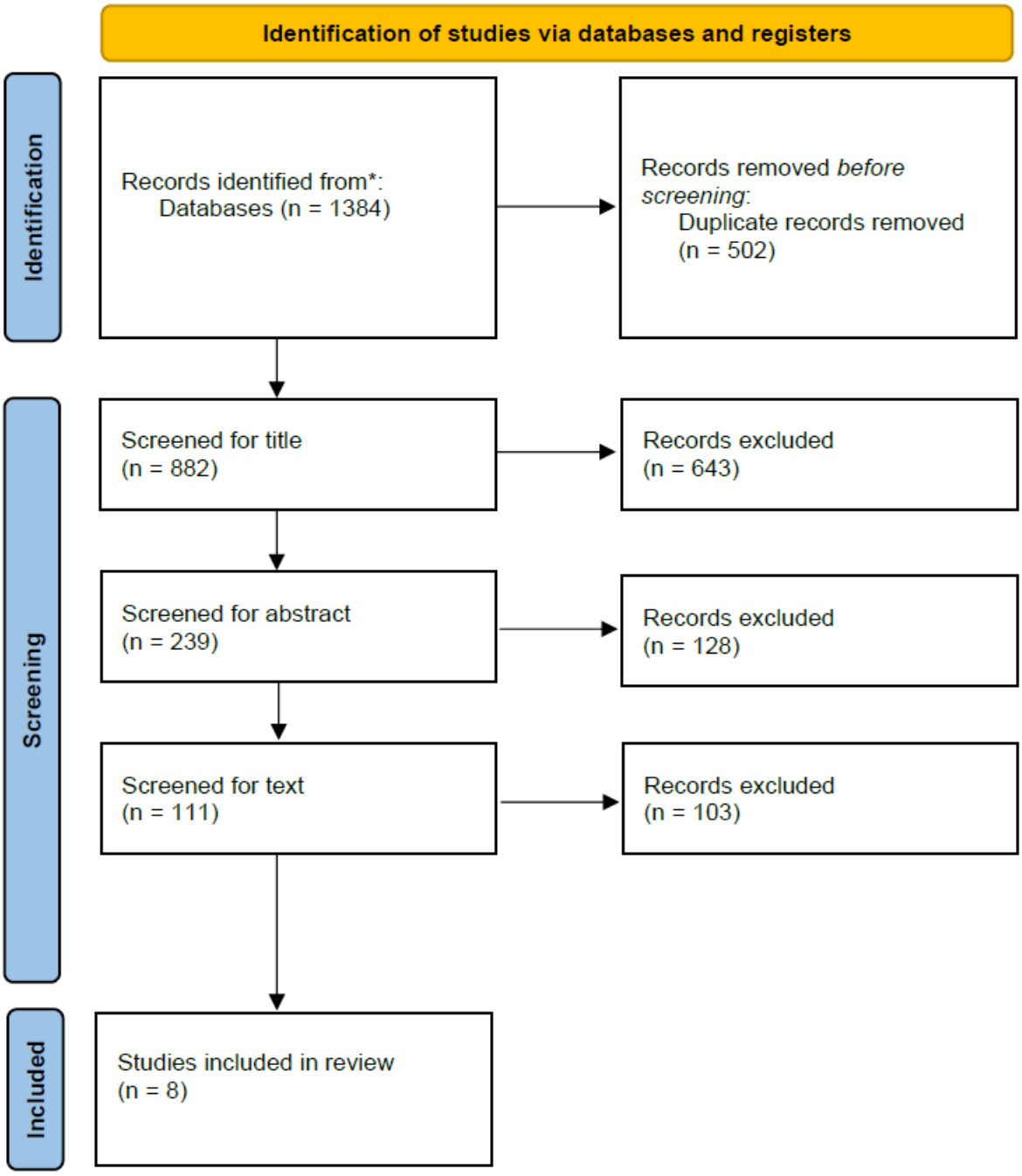


Figure 1: Search strategy

Data collection

The study characteristics of all included studies are provided in an overview table in Appendix 3. From the selected reviews, we extracted the author, study design, country, inclusion criteria, number of studies, population characteristics, comparison characteristics and outcome characteristics, as well as the relative risk (RR) and odds ratio (OR). We did not include the comparison characteristics in our overview table, as it is the same for all studies. The study designs of the primary studies were included as well.

Quality of the included reviews

The assessment of the systematic reviews was done using the AMSTAR II tool, which uses 16 criteria to measure the quality of the study. The tool evaluates whether the study has any weaknesses. High-quality studies are considered to have no weaknesses at all, medium-quality studies have more than one noncritical weakness, low-quality studies have one critical flaw, and very low-quality studies have more than one critical flaw.(5) Two researchers (HM and GM) conducted the AMSTAR II assessment. The full assessment per article is not included in this paper but can be provided upon request.

Of the 8 selected articles, 2 were rated high-quality, 2 were rated low-quality, and 4 were rated critically low-quality.

Neilson et al. and Neil-Sztramko et al. are the only two reviews of high quality, according to the AMSTAR II analysis. Only one weakness was found in each of these articles respectively: Neilson et al. did not thoroughly discuss their study design selection and Neil-Sztramko et al. did not report on the funding of their included studies.

Coletta et al. and Wu et al. are of low quality. None of the authors provided a list of excluded articles, nor a justification for why they were excluded. Their risk of bias assessment was only partially satisfactory. Neither of the reviews provided the sources of funding for the included articles. In addition, Wu et al. did not provide the information for their own funding either and did not describe the study setting, nor population of its included studies in detail, while Coletta et al. did not explain the selection of the study designs for inclusion of the review.

In accordance with the AMSTAR II analysis, 4 reviews were of critically low quality. These were the studies of Gao et al., Pizot et al., Pooralajal et al. and Daly et al. . The authors of these reviews did not provide a list of excluded articles; nor did they assess the risk of bias (or they did, but not in a way that was satisfactory); nor did they report funding of the included studies. Daly et al. did not provide a time frame for follow-up, nor did they provide a reason for study selection. Due to their critically low AMSTAR II score, we have not included these 4 reviews in our analysis and final conclusion.

A full overview of the weaknesses is provided in table 1.

Article	AMSTAR II Score	Weaknesses
Neilson et al.	HIGH	* Authors did not thoroughly discuss study design selection
Neil-Sztramko et al.	HIGH	* Authors did not report on funding of included studies
Coletta et al.	LOW	* Authors did not explain the selection of the study designs for inclusion of the review * Authors did not provide a list of excluded articles nor justification for why they were excluded * Risk of bias assessment was only partially satisfactory * Did not provide information concerning funding for individual studies

Wu et al.	LOW	* Authors did not provide a list of excluded articles nor justification for why they were excluded * Did not provide information concerning funding for individual studies, nor for their own article * Risk of bias assessment was only partially satisfactory * Included studies were described, but there was no detailed description of study setting, nor population
Daly et al.	CRITICALLY LOW	* There was no time frame for follow-up of the study * There was no explanation of study type selection * There was no clear study selection or extraction of data in duplicate * Authors did not provide a list of excluded articles nor justification for why they were excluded * Authors did not assess risk of bias * Authors did not provide information concerning funding for individual studies * Heterogeneity was not discussed
Gao et al.	CRITICALLY LOW	* Literature search was not exhaustive; authors did not consult experts in the field, nor searched study registries or grey literature * Authors did not provide a list of excluded articles nor justification for why they were excluded * Authors did not describe included studies in exhaustive detail * Authors did not describe selection bias, nor confounding bias * Authors did not provide information concerning funding for individual studies
Pizot et al.	CRITICALLY LOW	* Literature search was not exhaustive; authors did not consult experts in the field, nor searched study registries, bibliographies or grey literature * Authors did not provide a list of excluded articles nor justification for why they were excluded * Authors did not assess risk of bias from confounding bias * Authors did not provide information concerning funding for individual studies
Pooralajal et al.	CRITICALLY LOW	* Literature search was not exhaustive; authors did not consult experts in the field, nor searched study registries, bibliographies or grey literature * Authors did not provide a list of excluded articles nor justification for why they were excluded * Authors did not describe included studies in exhaustive detail * Authors did not assess risk of bias from confounding bias * Authors did not provide information concerning funding for individual studies

Table 2: AMSTAR II Score analyzing the weaknesses of the selected reviews.

Funding bias

Funding bias is the risk of forming a specific conclusion to satisfy a source of funding. Risk of funding bias was low in most of the 8 studies, apart from Pooralajal et al., where one of the data collectors may have had a monetary incentive.

Wu et al. stated there was no conflict of interest, but they failed to declare a source of funding. Therefore, Wu et al. was the only review among the 4 reviews with a low or high AMSTAR II score that had a minor risk of funding bias.

Further, the researchers of Daly et al. provided sources of income from external medical companies, though not the source of funding for the individual studies.

Finally, Neil-Sztramko et al. and Neilson et al. indicated that they were mostly funded by scholarships of various health care foundations and organizations.

Confounding bias

Confounding bias in the reviews stems from the articles used, and whether they were adjusted for specific, often related, risk factors. All included articles provided some form of adjustment for confounding factors. The main adjusted confounding factor is BMI.

Neil-Sztramko et al. included a list of their discussed articles and whether they were adjusted for other risk factors. Unfortunately, none of the 8 articles provided adjusted results for obesity.

Neilson et al. adjusted for confounding factors by also analyzing sub-groups of studies, in which each sub-group was treated as a different study in random-effects models to reduce within-study confounding. The authors admit that the data used in the article must be taken with a grain of salt, as statistical adjustment for confounding factors, such as non-recreational activity, is crucial for interpreting the data.

Coletta et al. evaluated the study quality of the included studies, partially for confounding factors. They provided a list of the articles where the intensity of confounding factors or adjustment thereof was listed. An exhaustive table was provided, discussing which adjustments were made for which confounding factors. The confounding factors that were adjusted for in the articles the most were: BMI, age, parity, age of menopause.

Wu et al. states that most of the articles included were adjusted for BMI. They admit that observed associations were at risk for unmeasured or residual confounding factors.

33 of the used articles in Pizot et al. were adjusted for BMI. Other risk factors were not discussed in the review. (6)

Gao et al. acknowledged the problem of including multivariate analyses in which different studies adjusted for different risk factors. (7)

Pooralajal et al. and Daly et al., did not provide clear information on the adjustment for confounding in its review.

Publication bias

Most reviews used the Begg's test and the Egger's test to screen their articles for publication bias.(8) A p-value lower than 0.05 indicates a high risk of publication bias.(9) Most reviews declared there was no evidence of publication bias.

Neil-Sztramko et al. discussed the possibility for publication bias: they state this data was largely unavailable and as such was not included in their review. No Begg's, nor Egger's tests were conducted.

Coletta et al. and Daly et al. did not provide any information concerning publication bias.

Table 3 provides an overview of the different biases.

Articles	**Funding bias**	**Confounding bias**	**Publication bias**	
			Begg's test	**Egger's test**
Coletta et al.	Low	Low	Not executed	Not executed
Daly et al.	Low	High	Not executed	Not executed
Neilson et al.	Low	Low	P < 0.001	P < 0.001
Neil-Sztramko et al.	Low	Low	Not executed	Not executed
Gao et al.	Low	Low	P = 0.488	P = 0.909
Pizot et al.	Low	Low	P = 0.96	P < 0.01
Pooralajal et al.	High	High	P = 0.677	P = 0.136
Wu et al.	Moderate	Moderate	Not executed	P = 0.07

Table 3: bias overview, not every review reported a clear Begg's or Egger's test, nor an alternative test

Evaluating the heterogeneity of included systematic reviews

The different reviews had a disparity in their selection of articles. One of the reasons was a slightly different study population.

Gao et al. included studies concerning Chinese women.

Daly et al. limited their discussion to premenopausal women.

Coletta et al. (2020) only included studies with women with BRCA1/2 variants.

The study population for Neilson et al. was broad, including both pre-and postmenopausal women, but with sub-group analyses of these groups.

Pooralajal et al. also included women of all ages.

Pizot et al. excluded studies where the type of physical activity was not specified (i.e., occupational or non-occupational), furthermore sub-group analyses on the effect of HRT (Hormone Replacement Therapy) and the effect of physical activity were also discussed.

Other reviews had fewer selected studies because of their broader scope. Gao et al. also focused on tea and alcohol consumption as risk factors. Only 15 of the 39 discussed studies focused on the effects of physical activity. Daly et al. discussed a whole array of both modifiable and non-modifiable risk factors: BMI, alcohol consumption, smoking, night shift work and socioeconomic status, hormonal contraceptives, pregnancy,... Coletta et al. discussed both breast cancer and ovarian cancer, dietary habits and weight status were also discussed as risk factors. Pooralajal et al. discussed a whole array of risk factors including smoking, alcohol intake, breast feeding, parity, BMI,... of all 197 discussed articles, 16 discussed the influence of physical activity.(10)

Coletta et al. and Daly et al. did not provide an exhaustive search strategy and description of inclusion criteria.

An overview is provided in table 4.

Article	# of articles	Reasons for heterogeneity
Daly et al., 2021	**3**	* Undefined inclusion criteria * No exhaustive literature search * Other risk factors also discussed * Includes both pre-and postmenopausal women
Coletta et al., 2020	**18**	* Only women with BRCA1/2 variants were included * Authors did not explain the selection of the study designs for inclusion of the review * Besides breast cancer, ovarian cancer discussed as well * Other risk factors also discussed
Neil-Sztramko et al., 2017	**29**	*Both pre- and postmenopausal women included
Pizot et al., 2016	**38**	* Only includes studies where type of physical activity is specified * Further focus on studies where HRT use is included * Both pre- and postmenopausal women included
Gao et al., 2013	**15**	* Only Chinese women included * Other risk factors also discussed * Both pre- and postmenopausal women included
Wu et al., 2013	**31**	* Both pre- and postmenopausal women included * Includes studies with prospective designs only
Neilson et al., 2016	**67**	* Includes pre-and postmenopausal women, as well as sub-group analyses in these categories

Pooralajal et al., 2021	**16**	* Other risk factors also discussed (of all 197 included articles, only 16 pertain to physical activity) * Both pre- and postmenopausal women included

Table 4: Reasons for heterogeneity overview

Assessment of study overlap

In order to analyze the study overlap of the selected reviews, we generated a citation matrix as described in Hennessy et al.(11) The full matrix is provided in Appendix 1.

A graphical cross tabulation was made of all included reviews (in columns) and their included primary studies (in rows). The degree of overlap can be quantified with a measure known as the corrected covered area (CCA). The CCA is a percentage that is calculated using the following formula:

$$(N-r)/(rc-r)$$

N is the number of publications included in evidence synthesis, r is the number of rows, and c is the number of columns. Overlap is categorized as very high (CCA >15%), high (CCA 11-15%), moderate (CCA 6-10%), or low (CCA 0-5%). The calculation of the overlap is provided in Appendix 2.

Most studies had a low to moderate overlapping score. For the studies with a high to very high CCA, we provided an overview of the differences between studies with a high to very high CCA in table 5. Studies with a higher quality rating or larger sample size are more likely to be included in our results.

Articles	**CCA-percentage**	**Differences**
Neilson et al. vs Neil-Sztramko et al.	21,52%	Neilson et al. has a larger sample size and included newer studies than Neil-Sztramko et al.
Neilson et al. vs Pizot et al.	31,40%	Neilson et al. has a larger sample size and is of better overall quality than Pizot et al.
Neilson et al. vs Wu et al.	22,50%	Neilson et al. has a larger sample size and is of better overall quality than Wu et al.
Neil-Sztramko et al. vs Pizot et al.	33,93%	Pizot et al. has a larger sample size, yet Neil-Sztramko et al. is of better overall quality
Neil-Sztramko et al. vs Wu et al.	33,33%	Neil-Sztramko et al. is of higher AMSTAR II quality than Wu et al.
Pizot et al. vs Wu et al.	57,14%	Pizot et al. has a larger sample size than Wu et al.

Table 5: Comparison of studies with high CCA differences and their differences

Risk of bias of primary studies

Most of the 4 reviews included a risk of bias assessment of the primary studies, this was done either by choosing a study design with an inherent low risk of bias or by using a specific tool.(12)

Coletta et al. performed a risk of bias assessment using the Quality Assessment Tool for Quantitative Studies.(13) With this tool, 6 different components are evaluated in order to determine overall study quality: selection bias, design, confounders, blinding, data collection method, withdrawal/dropouts. Most of the evaluated studies were considered to have a strong quality score.

Neil-Sztramko et al. used separate tools to assess the risk of bias for cohort and case-control studies. These tools use a scale to determine the risk of bias. A higher score indicates a higher risk of bias.(14) The authors of the study provide references for the used tools. These references, however, do not provide sufficient

information to find the associated study or tool. The results of their risk of bias analysis are only available upon request.

Neilson et al. did not provide a risk of bias analysis of the primary studies.

Wu et al. did not thoroughly examine the risks of bias in the primary studies. They did, however, rely on the study design to be less prone to have recall bias and selection bias.

Quality of evidence in included reviews

To assess the quality of the evidence load of the discussed reviews, we used the GRADE analysis on the 4 reviews of low or greater quality as shown by the AMSTAR II analysis: Neilson et al., Neil-Sztramko et al., Wu et al. and Coletta et al.(15) GRADE is the most widely adopted tool for quality appraisal.(16) The tool has 4 levels of evidence: very low, low, moderate and high. Studies start with a certain level of evidence, depending on the study design.(17) 8 different domains are evaluated to either downgrade or upgrade the final GRADE. For the downgrades of the quality of evidence, we used the checklist as drafted by Meader et al. to ease the evaluation of the grade of evidence.(18) All of the primary studies in the included systematic reviews are observational studies (Cohort studies and case control studies). As such, the starting point of every rating was low grade, as no randomization of results is possible. In 3 of the meta-analyses inconsistency was measured by the I^2 measure of Higgins et al., in which a 0, 25, 50, 75, respectively mean no, low, moderate and high inconsistency.(19)

Articles	Study Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrades	Final Grade
Neilson et al.	Low Grade (Observational)	No serious	Serious	No serious	No serious	Serious	Dose-response relationship present	Very Low
Neil-Sztramko et al.	Low Grade (Observational)	No serious	No serious	No serious	No serious	Serious	Dose-response relationship present	Low
Wu et al.	Low Grade (Observational)	No serious	No serious	No serious	No serious	No serious	Dose-response relationship present	Moderate
Coletta et al.	Low Grade (Observational)	Serious	Serious	No serious	No serious	Serious	None	Very Low

Table 6: GRADE assessment

The final grades of the 4 evaluated studies were mainly impacted as follows:

Neilson et al. based their information on case-control studies and cohort studies. There was a downgrade due to inconsistency, as the load of evidence showed great heterogeneity (I^2 score >70%). When adjusted for cohort studies only, heterogeneity was lower, but still moderate (I^2 = 41.1%). Publication bias was evaluated using the Begg's and Egger's tests. The bias was deemed serious enough to downgrade the study again. As for upgrading opportunities, the study showed a dose-response relationship between physical activity and breast cancer reduction. This, however, was not deemed enough to raise the grade from very low to low.

Neil-Sztramko et al. based their information on case-control studies and cohort studies. There was moderate heterogeneity in the analysis of each BMI group (I^2 between 28% and 67%). Sources of indirectness were low, outcomes were consistent, no surrogate outcomes were used. Publication bias was not evaluated, which constitutes a deficiency serious enough to downgrade the grade. The reported dose-response relationship, on the other hand, raises the grade from very low to low.

Wu et al. based their information on (prospective) cohort studies. Low to moderate inconsistency was found in most of these studies. 2 of the 31 studies showed a higher heterogeneity. There was a dose-response relationship described between physical activity and breast cancer risk reduction. This raises the grade from low to moderate.

Coletta et al. confirm that there was a high between-study heterogeneity, without providing a I^2 test. Sources of indirectness were low and no surrogate outcomes were used in all discussed reviews, however, the outcomes were inconsistent. This amounted to a very low grade.

Coletta et al. Was the only study to have a moderate grade of imprecision, as only a small number of studies (n=4) were discussed (although the number of participants in most of these studies can be considered to be sufficient). The foregoing in contrast to the other 3 reviews discussed, which each discussed over 10 studies and covering sufficient participants as well.

Publication bias was considered high with the Begg's and Egger's tests ($p<0.001$) in Neilson et al.. Coletta et al. and Neil-Sztramko et al. did not provide an analysis of publication bias. Publication bias was low in Wu et al., but there were other sources of potential bias (see infra).

The final grade is displayed in table 6: Wu et al. has a moderate GRADE score, Neil-Sztramko et al. has a low GRADE score and both Coletta et al. and Neilson et al. have a very low GRADE score.

Results

Effect on breast cancer

After filtering for title, abstract and full text, we included 8 systematic reviews and meta-analyses concerning the influence of physical activity on the incidence of breast cancer. Of these 8 studies, 4 were of sufficient quality to implement in our results. The quality was evaluated as a combination of the AMSTAR II scores and present biases. The included studies are: Neil-Sztramko et al., Coletta et al., Neilson et al., and Wu et al. .

Neil-Sztramko et al. analyzed 29 papers and made subgroup analyses. Their meta-analysis showed a reduction in breast cancer incidence in post-menopausal women with high physical activity and a BMI under 30 kg/m^2. The effect was greater for women with a BMI under 25 kg/m^2, with a RR of 0.85 (95% CI 0.79, 0.92), compared to women with a BMI between 25 and 30 with a RR of 0.87 (RR 0.87, 95% CI 0.81, 0.93). The authors did not find a significant effect in the reduction of breast cancer incidence in premenopausal women.

Coletta et al. looked at the effect of physical activity on breast cancer and ovarian cancer with people carrying the BRCA 1 and 2 gene variants, as well as the effects of diet and weight management. 4 studies were included concerning physical activity. Physical activity in adolescence was found to show an inverse effect on the risk of breast cancer when there was moderate physical activity. High physical activity did not show a significant increase of effect.(20)

Neilson et al. described an overall inverse effect of higher intensity recreational activity with a premenopausal RR of 0.80 (0.74-0.87) and a postmenopausal RR of 0.79 (0.74-0.84. Inverse associations were weaker among postmenopausal cohort studies (RR = 0.90 (0.85-0.95)) and studies that statistically adjusted for nonrecreational activity (premenopausal RR = 0.91 (0.77-1.06), postmenopausal RR = 0.96 (0.86-1.08)). Among studies with overweight/obese women, there was an inverse association with postmenopausal (RR = 0.88 (0.82-0.95)), but not with premenopausal (RR = 0.99 (0.98-1.00)) breast cancer.(21)

Wu et al. found a significant reduction in breast cancer risk with both occupational and non-occupational activity. They also described an inverse linear relationship between breast cancer risk and physical activity. The effect seemed similar in both groups.

Study	Measure	Effect	RR	# Of studies
Coletta et al. (2020)	Moderate intensity physical activity in adolescence	Reduction in breast cancer incidence	Not described	4
Neil-Sztramko et al. (2017)	High intensity physical activity in Post-Menopausal Women	Reduction in breast cancer incidence	RR 0.85 (95% CI 0.79, 0.92)	29
Wu et al. (2012)	Physical activity	Reduction in breast cancer incidence	RR 0.88 (95% CI, 0.85 – O.91)	31
	Non-occupational activity	Reduction in breast cancer incidence	RR 0.87 (95% CI, 0.83-0.91)	27
	Occupational activity	Reduction in breast cancer incidence	RR 0.90 (95% CI, 0.83-0.97)	7
Neilson et al. (2015)	Moderate vigorous physical activity premenopausal women	Reduction in breast cancer	RR 0.80 (95% CI, 0.74 – 0.87)	43
	Moderate vigorous physical activity postmenopausal women	Reduction in breast cancer	RR 0.79 (95% CI, 0.74-0.84)	58

Table 7: results

Analysis of Subpopulations

Analysis of the effect of physical activity on breast cancer was not only performed on the general female population in the selected reviews, as several subpopulations were discussed as well. Mainly premenopausal and postmenopausal women were discussed as separate subpopulations. Perimenopausal women were not clearly discussed in any of the selected articles. Furthermore, Coletta et al. specifically reviewed literature pertaining to the subgroups of women with BRCA1/2 pathogenic germline variants and women without such variants. Finally, other discussed subpopulations were women with a lower BMI score (under 25 kg/m^2) and women with a higher BMI score (above 25 kg/m^2). Data on men with breast cancer was not discussed in any of the selected reviews.

Premenopausal women vs Postmenopausal women

3 of the selected reviews discussed the effect of physical activity on the incidence of breast cancer in both pre- and postmenopausal women. (Further details are shown in table 8)

Physical activity appears to have a significant impact on the reduction of breast cancer incidence in both premenopausal women and postmenopausal women. The effect caused by moderate physical activity was found to be quite similar in both groups, according to Neilson et al., with an overall effect size of about 20% in both subgroups. Neilson et al. found high heterogeneity in the results for premenopausal women and postmenopausal women as well, with a I^2 heterogeneity score of 71.1% and 76.1% respectively.

Other studies comparing menopausal status did not find such similar results. Wu et al. reported a less beneficial effect of physical activity in postmenopausal women when compared to premenopausal women. Neil-Sztramko et al. divided the subgroups of pre- and postmenopausal women, according to BMI. The effect of moderate physical activity was lower in every postmenopausal BMI subgroup when compared to the premenopausal BMI subgroups, suggesting that the effect of physical activity on the incidence of breast cancer is greater in premenopausal women (greater detail is given further in our article, as well as in table 9).

Study	Physical activity and Menopausal status Subgroup	Effect	RR	# Of studies
Coletta et al. (2020)	No specific data for pre- and postmenopausal subgroups was provided by authors			
Neil-Sztramko et al. (2017)	Results are discussed in table 9			
Wu et al. (2012)	Premenopausal	Reduction in breast cancer incidence	RR 0.77 (95% CI, 0.69-0.86)	6
	Postmenopausal	Reduction in breast cancer Incidence	RR 0.87 (95% CI, 0.87-0.92)	17
Neilson et al. (2015)	Premenopausal	Reduction in breast cancer incidence	RR 0.80 (95% CI, 0.74 – 0.87)	49
	Postmenopausal	Reduction in breast cancer incidence	RR 0.79 (95% CI, 0.76 – 0.84)	64

Table 8: results as related to menopausal status

Lower BMI score vs higher BMI score

BMI is another factor on which subgroup analyses were based in the discussed reviews. Neil-Sztramko et al. analyzed the effect of physical activity on breast cancer incidence in women with different BMI-scores. Both Wu et al. and Neilson et al. made subgroup analyses for BMI as well.

The breast cancer incidence reduction for women with a BMI under 25 kg/m^2 ranged between 15% and 28% when compared to non-exercising women.

The effect of physical activity on the reduction of breast cancer incidence in women with a higher BMI above 25 kg/m^2 is less clear: while Neil-Sztramko et al. reported a statistically significant effect of physical

activity on the reduction of breast cancer, Neilson et al. saw a statistically significant effect only in the subgroup analysis in postmenopausal women and Wu et al. found no significant effect at all.

Subgroup analysis results for women with a BMI score above 30 kg/m^2 showed negligible results.

Table 8 shows a more thorough description of the BMI subgroup analyses.

Study	Physical activity in BMI Subgroup	Effect	RR	# Of studies
Coletta et al. (2020)	Did not make a BMI subgroup analysis			
Neil-Sztramko et al. (2017)	BMI < 25 kg/m^2 Women in general	Reduction in breast cancer incidence	RR 0.78 (95% CI, 0.72 – 0.86)	28
	BMI > 25 kg/m^2 Women in general	Reduction in breast cancer incidence	RR 0.81 (95% CI, 0.74, 0.88)	28
	BMI > 30 kg/m^2 Women in general	No significant effect on reduction in breast cancer incidence	RR 0.90 (95% CI, 0.72 – 1.12)	9
	BMI < 25 kg/m^2 Postmenopausal	Reduction in breast cancer incidence	RR 0.85 (95% CI, 0.79 – 0.92)	12
	BMI > 25 kg/m^2 Postmenopausal	Reduction in breast cancer incidence	RR 0.87 (95% CI, 0.81 – 0.93)	12
	BMI > 30 kg/m^2 Postmenopausal	No significant effect on reduction in breast cancer incidence	RR 0.93 (95% CI, 0.76 – 1.13)	6
Wu et al. (2012)	BMI < 25 kg/m^2	Reduction in breast cancer incidence	RR 0.72 (95% CI, 0.65 – 0.81)	9
	BMI > 25 kg/m^2	No significant effect on reduction in breast cancer incidence	RR 0.93 (95% CI, 0.83-1.05)	8
Neilson et al. (2015)	BMI < 25 kg/m^2 Premenopausal	Reduction in breast cancer	RR 0.85 (95% CI, 0.73 – 0.99)	7
	BMI > 25 kg/m^2 Premenopausal	No significant effect on reduction in breast cancer incidence	RR 0.99 (95% CI, 0.98 – 1.00)	7
	BMI < 25 kg/m^2 Postmenopausal	Reduction in breast cancer incidence	RR 0.84 (95% CI, 0.77 – 0.92)	15
	BMI > 25 kg/m^2 Postmenopausal	Reduction in breast cancer incidence	RR 0.88 (95% CI, 0.82 – 0.95)	12

Table 9: results according to BMI

Women with BRCA1/2 pathogenic germline variants vs women without

Coletta et al. made a subgroup analysis based on women with the pathogenic germline variants of BRCA1/2 and those without such variants. The authors did not report their own relative risks, as they considered the included studies to be too limited. They discussed the 4 studies concerning BRCA1/2 mutations and concluded that the evidence load was insufficient, but the results indicated a reduction of

breast cancer incidence in both pre- and postmenopausal women with BRCA1/2 variants, with a 40% risk reduction in the highest-intensity physical activity groups.(22,23)

Study	Physical activity in BRCA1/2 Subgroup	Effect	RR	# Of studies
Coletta et al. (2020)	BRCA1/2 +	Reduction in breast cancer incidence	Lack of studies	4
	BRCA1/2 -	Reduction in breast cancer incidence	Lack of studies	4

Table 9: results pertaining BRCA1/2

Amount, type and timing of physical activity

The selected reviews also made distinctions in the amount or type of physical activity that was performed and its effect on the incidence of breast cancer. The main distinction was made in the amount or intensity of physical activity. Other distinctions are the timing of the physical activity, as well as the type of physical activity (e.g., occupation vs non-occupational physical activity).

Amount of physical activity

Physical activity is difficult to quantify in retrospective studies, as no standardized training regime or other factors can be instituted. Several articles quantify activity in vague terms of low, moderate and vigorous physical activity, which, when analyzed, showed a dose-response relationship, with moderate to vigorous activity having a great breast cancer risk reduction when compared to low activity.(14,20,21)

Another way to quantify physical activity, is by using the metric of MET-h/week. MET, as postulated by Ainsworth et al., stands for Metabolic Equivalent of Task, it measures how many times the energy expenditure of a specific activity compares to the energy expenditure of a person in resting. For example, desk work or slowly walking, are less than 3 METs, yoga and house work are between 3 and 6 METs and more intense activities, such as running, basketball and cycling, are more than 6 METs.(24) Neilson et al. used this metric to analyze the effect of physical activity. Coletta et al., Wu et al. and Neil-Sztramko et al. discussed several studies in which the measure of MET-h/week was also used.(12,14,20)

A dose response relationship between increasing physical activity and decreasing breast cancer risk was seen by Neilson et al., Wu et al. and Neil-Sztramko et al.(12,14,21) This inverse effect graphs as a steep slope that shallows out at 20-30 MET-h/week as shown in figure 2 by Neilson et al.. (21)

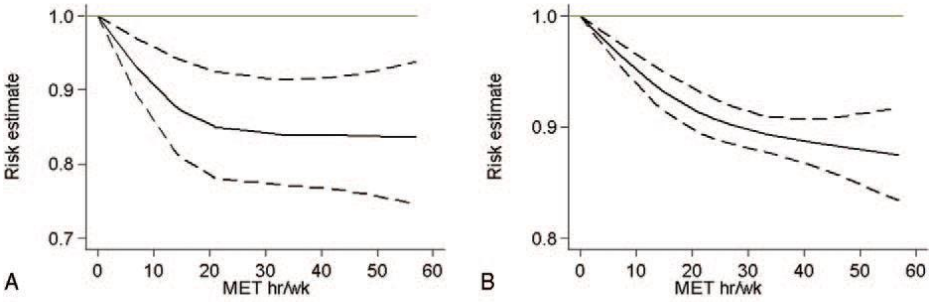


Figure 2: Dose response curve of premenopausal (A) and postmenopausal (B) risk reduction vs MET hr/week as developed by Neilson et al. The effect of physical activity shallows out at 20-30 MET-h/week.

Type of physical activity

Some studies make note of a possible distinction between the effect occupational and non-occupational activity. Non-occupational activity consists of both household tasks and recreational activity. Wu et al. is the only review out of our selection that made a specific analysis based on these subgroups. Both the effect of occupational and non-occupational activity was reported to have a similar statistically significant inverse effect on breast cancer incidence, with a relative risk of 0.90 and 0.87 respectively.(12) Neil-Sztramko et al. and Coletta et al. made sure to adjust their results for occupational activity as a possible confounder.(14,20)

Timing of physical activity

The life period during which physical activity took place was also considered as a possible influencing factor in several studies.

Of our selected reviews, only Wu et al. made a specific subgroup analysis based on the timing of physical activity. They categorized life periods in 4 different age groups: <25 years (RR = 0.92), 25-50 years (RR = 0.89), >50 years (RR = 0.88) and throughout follow-up (RR = 0.86). As such, they report that physical activity has a positive influence on the reduction of breast cancer incidence within all age groups.(12) Coletta et al. noted that the age of the women could have an effect on breast cancer incidence, but did not make an analysison the subject matter due to the low amount of studies discussed.(20,22,23,25)

Discussion

The included reviews concluded that there was a significant effect of physical activity on the reduction of breast cancer incidence.

The four main studies we included in the results were selected by their high quality rating and their assessed risk of bias. Although all of these studies showed that physical activity leads to a reduction of the incidence of breast cancer in both pre- and postmenopausal women, they reported differing results when comparing the two groups. Neilson et al. concluded that the breast cancer risk reduction was similar for both groups (around 20%). The other reviews, however, found that physical activity has a slightly smaller breast cancer risk reducing effect in postmenopausal women, although their results on the extent to which this was the case differed. As such, more studies are needed to draw conclusions about whether or not physical activity has a different effect on breast cancer incidence depending on women's menopausal status and, if so, to which extent.

According to one of the main studies, a similar reduction of breast cancer incidence as a result of physical activity is found in women with a BRCA1/2 germline mutation had when compared to women without the BRCA1/2 germline mutation. However, this study also indicates that the evidence is limited and that more studies are needed to evaluate the effect.

Based on three of the main studies, differences in BMI influence the effect of physical activity on breast cancer incidence. For women with a BMI higher than 30 kg/m^2, the risk reduction seems to be negligible in both pre-and postmenopausal women. The risk reduction is minimal for women with a BMI score between 25 kg/m^2 and 30 kg/m^2, though the discussed reviews have differing reports on this matter. Wu et al. did not see any significant result, and Neilson et al. did not see significant results in premenopausal women with a BMI higher than 25 kg/m^2. The effect of physical activity on breast cancer risk reduction was significant in premenopausal and postmenopausal women in all selected reviews. These results

indicate that BMI is an independent risk factor and may be a significant confounder if not corrected for.(11,18) An explanation to why women with a BMI above 25 kg/m² would have a more limited benefit or even no benefit of physical activity can be found in the higher percentage of adipose tissue. Adipose tissue influences the risk of breast cancer in several ways. Firstly, adipose tissue has several endocrine secretions that may influence the development of breast cancer. Adipose tissue produces estradiol and is the largest source of estradiol in postmenopausal women. This increases the amount of aromatase activity in the breast, which in turn dysregulates the estrogen signaling mechanism in the breast.(11,23) Secondly, women with a higher BMI (> 25 kg/m²) may tend to over-report their physical activity levels more than women with a lower BMI (< 25 kg/m²). This may downplay the effect physical activity has on health benefits.(11,24) Thirdly, people with a higher BMI (> 25 kg/m²) may have other habits and routines that could be considered to be confounding factors, such as: worse dietary habits, more prone to be of lower socio-economic status, more likely to be smokers, more likely to drink more units of alcohol… All factors one may have to adjust data for.(25,26)

Physical activity was divided into several subgroups, mainly with regards to the amount of physical activity performed. Generally, more rigorous physical activity showed a greater effect on the reduction of breast cancer incidence. To quantify the amount of physical activity, several reviews used the metric of MET-h/week, in which 20-30 MET-h/week showed a significant inverse effect. Above 30 MET-h/week, the effect of physical activity reached a point of diminishing returns. Although both occupational and non-occupational physical activity had a significant effect, the amount of the physical activity seemed to be of greater importance than the type of physical activity. Adjusting for occupational physical activity/general activity versus recreational activity showed a lower effect of intensity of physical activity on the reduction of breast cancer incidence. As proposed by Neilson et al. the reason for this may be confounded by a generally more active lifestyle influencing the results. The timing of the physical activity seemed to be of lesser importance, with statistically similar significant results in every age group.

The effect of physical activity on the incidence of breast cancer in men was not discussed in any of the selected reviews. Although the incidence of breast cancer in men is much rarer and although one might assume the effect of physical activity on the incidence of breast cancer in men could be similar as in women, more studies are needed to make an informed conclusion in this matter.

However, there are several caveats in discussing the results as reported. The first main caveat is the quality of the reviews, based on the AMSTAR II analysis and the GRADE analysis. After the initial assessment of the reviews with the AMSTAR II tool, we concluded that only two of the included reviews could be graded as a high-quality review, while two others were to be graded as low-quality and four others as very low-quality. After eliminating the four very low-quality reviews in our main analysis, the GRADE analysis showed an evidence load of moderate quality for only one of the four remaining reviews, while the others had a low to very low GRADE score. Thusly, of the four reviews that, based on the AMSTAR II analysis, were of low or high quality, three were lacking in high grade evidence, based on the GRADE analysis. Secondly, multiple possible sources of potential bias were present in all reviews. Finally, only one review discussed prospective studies, which may generally provide for more reliable results. However, admittedly, this type of studies is hard to conduct with a research question as broad as the effect of physical activity on the incidence of breast cancer, as such research requires a lot of resources and time, especially when the study design involves long-time follow-up, which in turn increases the risk for attrition and as such for attrition bias.

There were several limitations in the general creation of our umbrella review we should put forward as well. Our initial intent was to discuss the effect of physical activity on the incidence of cancer in general, after which we narrowed our focus to the effect on the incidence of breast cancer in particular. This is why our primary search was not specific to breast cancer. Also, as it was our first endeavor in creating an umbrella review, we did not have the same experience as someone who writes articles as a vocation.

Conclusion

In conclusion, physical activity seems to have a significant positive effect on the reduction of breast cancer incidence. In both pre-and postmenopausal women, as well as in women with BRCA1/2 mutations. As a primary physician, it is one of our duties to promote the health of our patient population. A big part of this is preventative medicine.(30) The promotion of physical activity should be one of the pillars of preventative medicine. Not only to prevent breast cancer, but also for the numerous other health benefits entailed by physical activity. The amount of physical activity that one must promote to their patients as a primary physician, does not differ greatly from the amount one should already promote for other health benefits. However, more studies of a higher quality and with a higher-quality data evidence load needed to confirm this conclusion.

Reflection on group process and own contributions

Martijn

Most of our paper was created with additions from both Michaël and I, alternating between who worked on what specific part. That way we were able to have a different insight and/or perspective on each specific part of the paper. As such, determining who wrote each specific part of the paper is rather difficult. For example, I started the grading of the papers with the GRADE Analysis tool, but when completed, Michaël reviewed and edited the final analysis with his own insights and knowledge on the matter. Other times, one of us collected the data from the multitude of studies, while the other inserted said data in a table.

We started our paper quite ambitiously by wanting to describe the effect of physical activity on cancer in general. But after poring through all the articles and data, and in consensus with our co-promotor and promotor, we deemed this too ambitious of a task. Ultimately we settled on researching the effect of physical activity on breast cancer as our main discussion point and left the other kinds of malignancies for other researchers to discuss. We chose to study breast cancer mainly because of the greater number of articles based on the topic, as well as the high social awareness on the topic and the preventative measures we come in contact with on a weekly basis in general practice. Another reason was the availability with studies on the topic, a lot of other kinds of malignancies had less available studies discussing the effects of physical activity. Another part where I contributed greatly was the separation of the population groups and the analysis of the kind, timing and intensity of physical activity was discussed.

Our collaboration was very amicable, though maybe should have been more streamlined with a more consistent and consequent approach from the beginning. Luckily, our promotor brought us in contact with a fantastic co-promotor, Dr. Anne-Catherine Vanhove, who was of great help to us in the development of our master paper. Dr. Vanhove showed and taught us very applicable and handy tips and tricks, based on her real life experience in the matter at CEBAM (amongst others, of course), and got us back on course when we had written things that might not have been as clear as we had hoped or if we deviated too much from the original intent of our paper. We had somewhat less direct contact with Prof. Patrik Vankrunkelsven, our head promotor, though the grand lines of our paper and the direction where we should let the paper go were decided upon in mutual discussion and agreement with Prof. Vankrunkelsven. We had more contact in the last year of the development of the paper; in hindsight more meetings in the earlier stages might have been beneficial for the momentum of the development.

As for the effect of our paper on the daily practice, it is limited. As cited in our discussion and conclusion, the quality of the included reviews and the grade of evidence of the discussed studies therein is limited. The general consensus was that physical activity had an inverse effect on the incidence of breast cancer, but more studies are needed to confirm this effect, as well as more analyses on certain subgroups (like men) should probably be performed. As for the amount of physical exercise needed for this effect, the amount does not differ too much of the physical activity proposed for other health benefits or the Food and Physical Activity Triangle as developed by the Flanders Institute for Healthy living. As such, the advice one should give to their patients does not differ much from the advice a good doctor should already give to patients for a good overall health and other specific health benefits, like the prevention of cardiovascular, diabetic and orthopedic problems.

If I would have to start the master paper all over again, with the knowledge and experience we now have in terms of creating an umbrella review, I would probably not pick and write about the same topic, nor would I chose the same type of research. In my honest opinion the results of this paper were less exciting than what I had hoped for, and the process of making an umbrella review/literature study less riveting than I had anticipated. If I would have to start all over again, I might pick a topic that was just a little bit more hands-on. Something that would be a little bit more specific and a little bit more practical and applicable for our master in Family Medicine as well. All in all, working with Michaël on this paper was great, we were very open in what we wanted to accomplish and very honest when we found shortcomings in our paper. It would be great to work with him again.

Michaël

As it often goes with writing extensive papers like these: it did not always go as we expected it to go. Martijn Himpens and I chose to work together not only because we had an interest in similar topics, but also because we had a similar work ethic. We had a proper conversation before deciding to work together on this paper, so that we both knew what to expect from each other, e.g., in terms of time commitment and contribution. I believe that partially thanks to this clear communication, we never had any problems or frustrations in the 3 years we have worked together on this project. Should it be that we had to do another group assignment, I would gladly work with Martijn again.

The process of working together went very well. We planned several online meetings during which we were working on our paper together simultaneously or discussing how to proceed in our research. Throughout the process, we found a good method of consistently working on our thesis. At the start, for instance, we did not have a specific division of tasks. However, as the process went along, we decided at the end of every meeting who would do what, and by what time each task should be completed. We made sure the tasks were evenly divided, and we were both flexible with each other's deadlines.

As we were both fairly inexperienced in writing scientific papers when we started out writing this paper, the process needed some adjustments as we went along. Thankfully we had good guidance provided by prof. Patrik Vankrunkelsven and dr. Anne-Catherine Vanhove. For example, at first, our goal was to make an umbrella review on the effects of physical activity on cancer in general. As we were doing our research, we found a good amount of reviews on this topic. The subject was promising, as there already were some studies and reviews done on the subject and we felt we could add our own input to it. We did, however, underestimate the workload when we made our first decision to investigate all cancers on physical activity. All in all, we found more than 100 applicable studies for all different kinds of cancer. We then categorized them for each specific cancer. We wanted to do a proper data analysis for each topic, but we realized that this would mean that we would need to fully analyze all the data from more than 100 reviews. Therefore, in consultation with prof. Vankrunkelsven and dr. Vanhove, we decided to focus on one specific cancer, as our review would otherwise be too broad and too cluttered. We were hesitant between discussing colon cancer or breast cancer, as they are both very frequent occurring cancers. Eventually we settled on breast cancer due to its high prevalence in the female population and its high impact on women of a relatively young age.

Martijn and I both had to do a lot of additional research to be able to write our paper. For example: our co-promotor, dr. Vanhove, suggested that it would add a lot of value to our paper if we were to do a GRADE analysis of each of the included reviews. Generally, doing such analyses does not take too much

time, but unfortunately neither of us had ever done a GRADE analysis before and thus had to learn how to do that from scratch. As we still had to educate ourselves in doing this type of analysis, it took us a week or two just to understand how a proper GRADE analysis is done. I definitely see this as a good physical activity and I'm glad I was able to learn something new as well. However, at the time it was quite frustrating to see that a seemingly small task took us quite a while to perform.

As for the clinical significance of our research, our paper does not reveal any groundbreaking new knowledge. We provided an overview of knowledge already available in a comprehensive manner, after verifying the quality of the sources setting out such knowledge. While this may not sound as exciting as researching something completely new or doing a clinical trial, the things I have learned from writing this paper will absolutely make me a better doctor. In particular, writing a review myself and performing multiple quality checks on other reviews using different tools has made me much more critical of other scientific publications. I know that I'm not an expert, but with the knowledge I have gained thanks to writing this paper, I will make better and more evidence based decisions in my daily practice. This skill of being critical towards any research that you come across, especially in this age of misinformation and a wide variety of biases, is, in my opinion, a very important one.

If I were to write another thesis, I would like it to be on the other end of the evidence spectrum: a randomized controlled trial or other type of clinical trial. It would be very interesting to learn about the strengths and pitfalls of doing your own hands-on research.

In conclusion, I am grateful to have been able to work with a great colleague like Martijn Himpens and it would be my pleasure to work with him again, but perhaps rather while conducting a different type of research next time.

Appendix

Appendix 1: CCA Matrix

	Coletta et al.	Daly et al.	Neilson et al.	Neil-Sztramko et al.	Gao et al.	Pizot et al.	Pooralajal et al.	Wu et al.
Cybulski C. et al., 2015	1	0	0	0	0	0	0	0
Dennis J et al., 2010	1	0	0	0	0	0	0	0
Dennis J et al., 2011	1	0	0	0	0	0	0	0
Gronwald J et al., 2006	1	0	0	0	0	0	0	0
Kim SJ et al., 2019	1	0	0	0	0	0	0	0
King MC et al., 2003	1	0	0	0	0	0	0	0
Ko KP et al., 2013	1	0	0	0	0	0	0	0
Kotsopoulos J et al., 2005	1	0	0	0	0	0	0	0
Lammert J et al., 2018	1	0	0	0	0	0	0	0
Lecarpentier J et al., 2011	1	0	0	0	0	0	0	0
Manders P et al., 2011	1	0	0	0	0	0	0	0
McGuire V et al., 2006	1	0	0	0	0	0	0	0
Moorman PG et al., 2010	1	0	0	0	0	0	0	0
Nkondjock A, Ghadirian P, et al., 2006	1	0	0	0	0	0	0	0
Nkondjock A, Robidoux A et al., 2006	1	0	0	0	0	0	0	0
Nkondjock A et al., 2007	1	0	0	0	0	0	0	0
Pijpe A et al., 2010	1	0	0	0	0	0	0	0
Qian F et al., 2019	1	0	0	0	0	0	0	0
Wu et al., 2013	0	1	0	0	0	0	0	0
Hardefeldt et al., 2018	0	1	0	0	0	0	0	0
Chen et al., 2019	0	1	0	0	0	0	0	0
Boeke et al., 2014	0	0	1	0	0	1	0	0
Brinton et al., 2014	0	0	1	0	0	1	1	0
Hallmarker et al., 2014	0	0	1	0	0	0	0	0
Bernstein et al., 1994	0	0	1	0	0	0	0	0
Friedenreich et al. 1995	0	0	1	0	0	0	0	0
McTiernan et al. 1996	0	0	1	0	0	0	0	0
Chen et al., 1997	0	0	1	0	0	0	0	0
Hu et al., 1997	0	0	1	0	0	0	0	0
Gammon et al., 1998	0	0	1	0	0	0	0	0
Enger et al., 2000	0	0	1	0	0	0	0	0
Moradi et al., 2000	0	0	1	0	0	0	0	0
Shoff et al., 2000	0	0	1	0	0	0	0	0
Verloop et al., 2000	0	0	1	1	0	0	0	0
Freidenreich et al., 2001	0	0	1	1	0	0	0	0
Gililand et al., 2001	0	0	1	0	0	0	0	0
Carpenter et al., 2003	0	0	1	0	0	0	0	0
Dorn et al., 2003	0	0	1	0	0	0	0	0
John et al., 2003	0	0	1	0	0	0	0	0
Steindorf et al., 2003	0	0	1	0	0	0	0	0
Yang et al., 2003	0	0	1	1	0	0	0	0
Bernstein et al., 2005	0	0	1	0	0	0	0	0
Magnusson et al., 2005	0	0	1	0	0	0	0	0
Kruk et al., 2007	0	0	1	0	0	0	0	0
Slattery et al., 2007	0	0	1	0	0	0	0	0
Sprague et al., 2007	0	0	1	0	0	0	0	0
Peplonska et al., 2008	0	0	1	1	0	0	0	0
Schmidt et al., 2009	0	0	1	1	0	0	0	0
Shin et al., 2009	0	0	1	0	0	0	0	0
Angeles-LLeranes et al., 2010	0	0	1	0	0	0	0	0
Ratna-Sinhe et al., 2010	0	0	1	1	0	0	0	0
Sheppard et al., 2011	0	0	1	0	0	0	0	0
McCullough et al., 2012	0	0	1	0	0	0	0	0
Kobayashi et al., 2013	0	0	1	0	0	0	0	0
Sanderson et al., 2015	0	0	1	0	0	0	0	0

Si et al., 2015	0	0	1	1	0	0	0	0
Hirose et al., 1995	0	0	1	0	0	0	0	0
D'Avanzo et al., 2013	0	0	1	0	0	0	0	0
Levi et al., 1999	0	0	1	0	0	0	0	0
Bissonauth et al., 2009	0	0	1	0	0	0	0	0
Suzuki et al., 2010	0	0	1	0	0	0	0	0
Kawai et al., 2013	0	0	1	0	0	0	0	0
Dirx et al., 2001	0	0	1	1	0	1	0	0
Catsburg et al., 2014	0	0	1	0	0	1	0	0
Hirose et al., 2003	0	0	1	1	0	0	0	0
Bardia et al., 2006	0	0	1	1	0	1	0	1
Eliassen et al., 2010	0	0	1	1	0	1	0	1
McTiernan et al., 2003	0	0	1	1	0	1	0	1
Breslow et al., 2001	0	0	1	1	0	1	0	1
Dallal et al., 2007	0	0	1	1	0	1	1	1
Moradi et al., 2002	0	0	1	1	0	1	1	1
Suzuki et al., 2011	0	0	1	1	0	1	0	1
Thune et al., 1997	0	0	1	1	0	1	1	1
Cerhan et al., 1998	0	0	1	0	0	1	0	1
Sesso et al., 1998	0	0	1	0	0	1	0	1
Wyrwich et al., 2000	0	0	1	0	0	1	0	1
Wyshak et al., 2000	0	0	1	0	0	1	0	0
Schnohr et al., 2005	0	0	1	0	0	1	0	1
Chang et al., 2006	0	0	1	0	0	1	0	1
Mertens et al., 2006	0	0	1	0	0	1	0	1
Navarro Silvera et al., 2006	0	0	1	0	0	1	0	1
Lee et al., 2001	0	0	1	0	0	1	0	1
Howard et al., 2009	0	0	1	0	0	1	0	1
Steindorf et al., 2013	0	0	1	0	0	1	0	0
Hildebrand et al., 2013	0	0	1	0	0	1	0	0
Hastert et al., 2013	0	0	1	0	0	1	0	0
Rosenberg et al., 2014	0	0	1	0	0	1	0	0
Dorgan et al., 1994	0	0	1	0	0	1	0	1
Colditz et AL., 2003	0	0	0	1	0	0	1	0
Maruti et al., 2008	0	0	0	1	0	1	0	1
Borch et al., 2014	0	0	0	1	0	1	0	0
Leitzmann et al., 2008	0	0	0	1	0	1	0	1
Patel et al., 2003	0	0	0	1	0	1	0	1
Peters et al., 2009	0	0	0	1	0	1	0	1
D'avanzo et al., 1996	0	0	0	1	0	0	0	0
Dallal et al., 2012	0	0	0	1	0	0	0	0
Kruk et al., 2003	0	0	0	1	0	0	0	0
Luoto et al., 2000	0	0	0	1	0	1	0	1
Pronk et al., 2011	0	0	0	1	1	1	0	1
Suzuki et al., 2008	0	0	0	1	0	1	0	1
Zang et al., 2003	0	0	0	0	1	0	0	0
Shannon et al., 2005	0	0	0	0	1	0	0	0
Wang et al., 2006	0	0	0	0	1	0	0	0
Jin et al., 2007	0	0	0	0	1	0	0	0
Kallianpur et al., 2008	0	0	0	0	1	0	0	0
Ren et al., 2008	0	0	0	0	1	0	0	0
Zhang et al., 2009	0	0	0	0	1	0	0	0
Gao et al., 2009	0	0	0	0	1	0	0	0
Shi et al., 2010	0	0	0	0	1	0	0	0
Dai et al., 2011	0	0	0	0	1	0	0	0
Xu et al., 2012	0	0	0	0	1	0	0	0
Hou et al., 2012	0	0	0	0	1	0	0	0
Yu et al., 2012	0	0	0	0	1	0	0	0
Lee et al., 2012	0	0	0	0	1	0	0	0
Paffenbarger et al., 1987	0	0	0	0	0	1	0	0
Steenland et al., 1995	0	0	0	0	0	1	0	0
Fraser et al., 1997	0	0	0	0	0	1	0	0
Moradi et al., 1999	0	0	0	0	0	1	0	0

Moore et al., 2000	0	0	0	0	0	1	0	0
Rintala et al., 2002	0	0	0	0	0	1	0	1
Rintala et al., 2003	0	0	0	0	0	1	0	0
Margolis et al., 2005	0	0	0	0	0	1	1	1
Tehard et al., 2006	0	0	0	0	0	1	0	1
George et al., 2010	0	0	0	0	0	1	0	0
Phipps et al., 2011	0	0	0	0	0	1	0	0
Baglietto et al., 2010	0	0	0	0	0	0	1	0
Baglietto et al., 2011	0	0	0	0	0	0	1	0
Bellocco et al., 2016	0	0	0	0	0	0	1	0
Bjerkaas et al., 2013	0	0	0	0	0	0	1	0
Ellingjord-Dale et al., 2017	0	0	0	0	0	0	1	0
Kops et al., 2018	0	0	0	0	0	0	1	0
Lahmann et al., 2007	0	0	0	0	0	0	1	0
Rockhill et al., 1999	0	0	0	0	0	0	1	1
Rod et al., 2009	0	0	0	0	0	0	1	0
Stahr et al., 2019	0	0	0	0	0	0	1	0
Rockhill et al., 1998	0	0	0	0	0	0	0	1
Steindorf et al., 2012	0	0	0	0	0	0	0	1
Total	**18**	**3**	**67**	**29**	**15**	**46**	**16**	**31**

Appendix 2: CCA calculation

	Number of publications (N)	Number of rows (r)	Number of reviews (c)	Percentage	Overlap
Study 1v2	21	21	2	0,00%	Low
Study 1v3	85	85	2	0,00%	Low
Study 1v4	47	47	2	0,00%	Low
Study 1v5	33	33	2	0,00%	Low
Study 1v6	64	64	2	0,00%	Low
Study 1v7	34	34	2	0,00%	Low
Study 1v8	49	49	2	0,00%	Low
Study 2v3	70	70	2	0,00%	Low
Study 2v4	32	32	2	0,00%	Low
Study 2v5	18	18	2	0,00%	Low
Study 2v6	49	49	2	0,00%	Low
Study 2v7	19	19	2	0,00%	Low
Study 2v8	34	34	2	0,00%	Low
Study 3v4	96	79	2	21,52%	High
Study 3v5	82	82	2	0,00%	Low
Study 3v6	113	86	2	31,40%	Very High
Study 3v7	83	79	2	5,06%	Low
Study 3v8	98	80	2	22,50%	Very High
Study 4v5	44	43	2	2,33%	Low
Study 4v6	75	56	2	33,93%	Very High
Study 4v7	45	41	2	9,76%	Moderate
Study 4v8	60	45	2	33,33%	Very High
Study 5v6	61	60	2	1,67%	Low
Study 5v7	31	31	2	0,00%	Low
Study 5v8	46	45	2	2,22%	Low
Study 6v7	62	57	2	8,77%	Moderate
Study 6v8	77	49	2	57,14%	Very High
Study 7v8	47	42	2	11,90%	High

Table 8: Study 1 = Coletta et al., study 2 = Daly et al., study 3 = Neilson et al., study 4 = Neil-Sztramko et al., study 5 = Gao et al., study 6 = Pizot et al., study 7 = Pooralajal et al., study 8 = Wu et al.

Appendix 3: overview of study characteristics

Author (year)	Study design	Country	Inclusion criteria	# of studies	N	Population	Intervention	Outcome	RR / OR	Study design of primary studies
Daly et al., 2021	Review	United Kingdom	Not defined	3	4.217.548	Premenopausal women	High intensity physical activity	Reduction in Breast Cancer incidence	(OR 0.73; 95% CI 0.65–0.81; P<0.001)	Meta-analysis
				3	4.217.548	Premenopausal women	Low intensity physical activity	Reduction in Breast Cancer incidence	(OR, 0.79; 95% CI, 0.72–0.86; P<0.001)	
Coletta et al., 2020	Review	USA	- Individuals with BRCA1/2 pathogenic germline gene variants - Evaluated weight status - Weight change - Dietary habits or physical activity in relation to ovarian or breast cancer risk - Published in English - Human subjects only	4	1.409	Women with BRCA1/2 variant	Moderate intensity physical activity in adolescence	Reduction in Breast cancer incidence	neither	Case-control, Retrospective cohort
Neil-Sztramko et al., 2017	Systematic review and meta-analysis	Canada	- Observational studies (cohort or case–control) - A primary exposure of physical activity (total, recreational, or leisure time) - A primary outcome of breast cancer incidence	29	1.212.978	Pre - and Postmenopausal women	High intensity physical activity in Pre- and Post-Menopausal Women	Reduction in breast cancer incidence No significant effect was found in pre-menopausal women	RR 0.85 (95% CI 0.79, 0.92)	Case-control, Cohort
Pizot et al., 2016	Meta-analysis of prospective studies	France	Eligible articles for this study had to: - report data on incident cases of breast cancer - report measurement of physical activity being occupational and/or non-occupational - have a prospective design	38	116.304	Pre-and postmenopausal women	High intensity physical activity	Reduction in breast cancer incidence	RR 0.88 (95% CI: 0.85, 0.90)	Prospective cohort

				6		Women without HRT use	High intensity physical activity without use of hormone replacement therapy (HRT)	Reduction in breast cancer incidence		
				6		Women with HRT use	High Intensity physical activity with HRT use	No significant effect	RR 0.97 (95% CI 0.88, 1.07)	
Gao et al., 2013	Systematic review and meta-analysis	China	- Case-control studies, cohort studies, prospective studies, and randomized controlled trials - Articles containing the following key words: breast cancer, breast carcinoma, breast tumor, breast neoplasm, mammary cancer, mammary carcinoma, mammary tumor, and mammary neoplasm; risk factors, behavior factor, tea, drinking, alcohol drinking, physical activity, and physical activity. - English or Chinese language - Chinese females only - A complete cross-table data of exposure with outcomes	15	100.452	Asian women	Regular physical activity	Reduction in breast cancer incidence	OR=0.73 (95%CI 0.63-0.85; I2 =77.3%; N=15).	Case-control, cohort
Wu et al., 2013	Meta-analysis of prospective studies	China	- Studies with Prospective design - RR with 95% CI provided - Duplicated data; study with most cases included - Number of cases and participants or person-years for each category of physical activity provided	31	63.786	pre-and postmenopausal women	Physical activity	Reduction in breast cancer incidence	RR 0.88 (95% CI, 0.85 - O.91)	Prospective cohort
				27	37.568	pre-and postmenopausal women	Non-occupational activity	Reduction in breast cancer incidence	RR 0.87 (95% CI, 0.83-0.91)	
				7	28.268	pre-and postmenopausal women	Occupational activity	Reduction in breast cancer	RR 0.90 (95% CI, 0.83-0.97)	

Neilson et al., 2016	Systematic review and meta-analysis	Canada	- Literature published to July 2015. - Cohort or case-control studies - No restrictions by language, date, or geographical location - Human subjects only - Studies pertaining only cancer survivors or males excluded - Studies with benign breast disease as outcome excluded - Articles with overlapping study populations, only one included - Case studies, cross-sectional studies, ecological studies, conference abstracts, unpublished work, newsletters and magazine-articles excluded	43	1.580.487	Premenopausal Women	Moderate vigorous physical activity	Reduction in (invasive or non-specific) breast cancer	RR 0.80 (95% CI, 0.74 - 0.87)	Case control, Cohort
				58	1.580.487	Postmenopausal Women	Moderate vigorous physical activity	Reduction in (invasive or non-specific) breast cancer	RR 0.79 (95% CI, 0.74-0.84)	
Pooralajal et al., 2021	Systematic review and meta-analysis	Iran	- Prospective cohort studies - Studies addressing the association between breast cancer and discussed risk factors	16	1.272.981	Women, regardless of age, race, ethnicity, geographical region	Moderate physical activity	Reduction in pathologically confirmed breast cancer	RR 0.90 (95% CI ,0.86, 0.95)	Prospective cohort

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